News in brief

Targets and mechanisms

First domain map of protein pathways completed

The first domain map of all the interactions of the known proteins found in one human protein domain family has been completed. Scientists at AxCell Biosciences Corp. (Princeton, NJ, USA) are attempting to map all the protein pathways in the human body to aid the identification of drugs that target pathways related to a specific disease, and thereby avoid those pathways associated with unwanted side effects. This study involved using advanced robotic screening techniques to identify more than 69,000 different protein interactions of the WW domain. Aberrations in the WW domain family are associated with disorders such as hypertension, muscular dystrophy and immunodeficiency.

Leroy Hood, Founder, President and Director of the Institute of Systems Biology (Seattle, WA, USA) said, 'AxCell has provided an interesting dataset for understanding protein signaling pathways… that could have implications for their role in a broad range of diseases.'

What's next for malaria genomics?

The sequencing of the malaria genome is close to completion, with the publication of two chromosome sequences and the imminent closure of the remaining 30 Mb of sequence. At a recent seminar on *Pathogen Genomes and Human Health* (Royal Society of Tropical Medicine and Hygiene, London, UK, 18 January 2001), the status of the Malaria Genome Project and its potential use was discussed by Alister Craig (Division of Molecular Biology and Immunology, Liverpool School of Tropical Medicine, Liverpool, UK).

The sequencing project was undertaken by The Institute for Genomic Research (TIGR; Rockville, MD, USA), The Sanger Centre (Cambridge, UK) and Stanford University (Palo Alto, CA, USA) and progress reports can be found at the following websites:

- http://www.sanger.ac.uk/Projects/P_falciparum;
- http://www.tigr.org/tdb/edb/pfdb/pfdb.html; and
- http://sequence-www.stanford.edu/group/malaria/index.html

The malaria genome consists of an estimated 6000 genes with a high level of polymorphism, a feature that has proved problematic for vaccine development. It is now hoped that features can be predicted from the malaria sequence, such as introns, DNA encoding signal peptides, transmembrane regions of proteins, coiled-coil domains, regulatory motifs and homologues in other species. However, Craig highlighted the problem of algorithmic analysis of the genome based on what we already know, thus genes that have not already been characterized would escape isolation.

The future, he feels, is in the use of microarrays, proteomics and bioinformatics to make use of the valuable resources the malaria genome can offer for the development of vaccines[1] and new therapeutics[2].

1 Hoffman, S.L. *et al*. (1998) From genomics to vaccines: Malaria as a model system. *Nat. Med*. 4, 1351–1353

2 Jomaa, H. *et al*. (1999) Inhibitors of the non-mevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science* 285, 1573–1576

Hyperthermia to help fight cancer

Recent research has shown that hyperthermia might offer a breakthrough for patients with head and neck cancer[1]. These squamous cell carcinomas are difficult to cure with radiation or chemotherapy because they tend to be partially dead and oxygen starved. Surgery, if possible, is often disfiguring. These tumours cannot take up adequate levels of chemotherapy drugs, and do not contain the required oxygen levels to enable radiation to work successfully. They emerge on CT scans as low-density metastatic nodes.

Hyperthermia might act as the activator required to increase the uptake of chemotherapy drugs in tumours and to sensitize tumours to radiation. Phase III clinical trials were carried out on 50 patients with head and neck squamous cell carcinoma and cervical node metastases[3]. It was found that hyperthermia acts as a radiosensitizer in the treatment of hypodense (at CT scan) metastatic nodes overcoming the radioresistance of necrotic, presumably hypoxic nodal metastases. Hyperthermia might therefore help to overcome the abysmal results obtained through traditional treatment of these tumours.

3 Amichetti, M. *et al.* (2000) Prognostic significance of cervical lymph nodes density evaluated by contrasted computer tomography in head and neck squamous cell carcinoma treated with hyperthermia and radiotherapy. *Int. J. Hyperthermia* 16, 539–547

Comparative genomics reveals potential targets for treating *Mycobacterium* infections

Genomic variation between members of the *Mycobacterium* genus have provided clues as to why *Mycobacterium* infections are so difficult to treat and eradicate. At a recent seminar on *Pathogen Genomes and Human Health* (Royal Society of Tropical Medicine and Hygiene, London, UK, 18 January 2001), Stephen Gordon from the Veterinary Laboratory Agency (Addlestone, UK) presented research on the comparative genomics of *Mycobacterium tuberculosis, M. leprae and M. bovis*[4–6].

M. tuberculosis infection (TB) is predicted to claim 30 million lives in the next ten years, despite the existing BCG vaccination programme. The sequencing of the genome of *M. tuberculosis* was completed in December 1997 and it is hoped that comparing the sequence with the attenuated *M. bovis* strain (BCG vaccine) might identify virulence factors in the *M. tuberculosis* genome. Gordon and colleagues have already found regions deleted in *M. bovis* that are responsible for virulence in *M. tuberculosis*, such as genes encoding phospholipase-3 and mycobacterial entry proteins. Furthermore, sequencing has shown variation in genes encoding proteins belonging to the PPE and PE family, which are thought to be antigenic determinants. There is no method currently available to effectively screen patients for TB, because it is impossible to distinguish between patients who have been vaccinated from those who are infected.

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Gordon and colleagues are using the same genomics techniques to investigate the pathogenicity of *M. leprae*, which, although predicted by the World Health Organization to be eradicated by 2000, caused 640,000 cases of leprosy in the past year. The group has already discovered metabolic differences between *M. leprae* and other mycobacteria, *M. leprae*-specific genes and mosaic regions that could have therapeutic implications for eradicating this devastating disease.

4 Brosch, R. *et al*. (2000) Comparative genomics of the *Mycobacteria*. *Int. J. Med. Microbiol*. 290, 143–152

5 Gordon, S.V. *et al*. (1999) Identification of variable regions in the genomes of tubercle bacilli using bacterial artificial chromosome arrays. *Mol. Microbiol*. 32, 643–655

6 Cole, S.T. *et al*. (1998) Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* 393, 537–544

Food for thought

New research has shown that persistent overeating in the obese leads to increased production of reactive oxygen species by leukocytes, increasing the risk of atherosclerosis and heart attack[7]. Researchers at the Diabetes–Endocrinology Center of Western New York, Kaleida Health, Buffalo, NY, USA) selected nine obese nondiabetic men and women with a mean body mass index (BMI) of 40.7 (a BMI of >30 is considered obese) who were placed on 1000-calorie diets for four weeks. The subjects were weighed and provided samples weekly during this period and were advised to continue a normal level of physical activity. At the end of the four weeks, blood samples showed a marked decrease in both markers of oxidative damage to lipids, proteins and amino acids and a >50% reduction in the generation of free radicals.

7 Dandona, P. *et al.* (2001) The suppressive effect of dietary restriction and weight loss in the obese on the generation of reactive oxygen species by leukocytes, lipid peroxidation and protein carbonylation. *J. Clin. Endocrinol. Metab.* 86, 355–362

Non-genotoxic stress induces mutation in cancer cells

Long-term genetic instability in cancer cells can occur without direct damage to DNA, a recent report has claimed[8]. The research by a group at Duke University Medical Center (DUMC; Durham, NC, USA) might help to explain how cancers become resistant to therapy or become more aggressive.

Mouse tumour cell lines were exposed to one of following stresses: ionizing radiation, hydrogen peroxide, high temperature, nutrient starvation and growth of the cell *in vivo* (in mice). Each type of stress caused deletion of a marker gene and alteration of repetitive sequences within both surviving cells and their non-exposed progeny. It is thought that if common treatments can induce such genetic instability, drug resistance might develop from the accumulation of mutations after treatment, rather than the clonal expansion of existing drug-resistant cells.

On the significance of these results, Mark Dewhirst (DUMC) commented that: 'If developing cancer depended on acquiring the right set of mutations by chance alone, no one would ever get cancer… there's been no convincing way to explain how the right mutations accumulate with enough frequency to lead to the incidence of cancer that is observed'. These latest findings might help

Clinical trials

Atragen denied approval by FDA

A new intravenous formulation of tretinoin for the treatment of acute promyelocytic leukemia (APL) has been denied approval by the Food and Drug Administration (FDA), announced its developers Aronex Pharmaceuticals (The Woodlands, TX, USA) recently. Atragen® a tretinoin liposome, was devised for patients for whom the present oral formulation is inappropriate. Aronex believes the principal reason why its application was not successful was a lack of data demonstrating an identifiable population of patients who need tretinoin and cannot take the oral formulation. Aronex will now apply to market Atragen in Europe as a treatment for APL, as well as investigating its other potential as a treatment for non-Hodgkin's lymphoma (currently in Phase III clinical trials), hormone-resistant prostate cancer (in Phase II trials), renal cell carcinoma in combination with interferon-α (in Phase I/II trials) and acute myelogenous leukemia (in Phase II trials).

Vaccine trials for malaria

Malaria vaccine trials in non-human primates are now underway as the result of a partnership between the Malaria Vaccine Initiative at PATH (Program for Appropriate Technology in Health, Seattle, WA, USA) and the Emory University Vaccine Research Center (Atlanta, GA, USA). The project, which will take place at the Yerkes Regional Primate Research Center (Atlanta, GA, USA) and sponsored by PATH, will involve multiple staggered trials to assess the safety, dosing and immunogenicity of several vaccines chosen from those developed by leading research institutions worldwide. The trial is being headed by Mary Galinski (Division of Infectious Diseases, Department of Medicine, Emory University, Atlanta, GA, USA), who is concurrently undertaking research into the genetics of *Plasmodium*. Genetic variation between strains of *Plasmodium* has previously hindered the development of an effective vaccine, and it is thought that, ultimately, several vaccines will be required to eliminate all forms of malaria. More information about malaria research and vaccine initiatives can be found at the homepage of the Malaria Foundation International (http://www.malaria.org) and the Malaria Vaccine Initiative website set up by PATH (http://www.malariavaccine.org).

our understanding of why there are numerous mutations in cancer cells, but more work is needed to understand the mechanism of non-genotoxic mutation.

8 Li, C-Y. *et al*. (2001) Persistent genetic instability in cancer cells induced by non-DNA damaging stress exposures. *Cancer Res*. 61, 428–432

Potent new HIV-1 entry inhibitor designed

A small protein, 5-Helix, has been developed that displays potent inhibitory activity against diverse HIV-1 variants and that could provide a basis for a new class of antiviral agents[9]. Researchers at the Howard Hughes Medical Institute (Chevy Chase, MD, USA), Whitehead Institute for Biomedical Research (Cambridge, MA, USA) and Merck Research Laboratories (West Point, PA, USA) designed this compound to bind to the C-peptide region of glycoprotein gp41, the part of the protein that binds the protein to the virus. Drugs that bind to this C-terminal portion of gp41 prevent the C- and N-terminals of the protein binding together, a process that is necessary for the virus to fuse its membrane to that of the host cell. The structure of 5-Helix is very similar to that of gp41 but with only five of the required six interconnected coils, which prompts it to bind to the C-terminal end of gp41 to complete the cluster of three hairpins.

However, John Moore (Weill Medical College, Cornell University, New York, NY, USA) warns that, even if 5-Helix or a related compound works *in vivo*, it is unlikely to dominate the market as it would be digested if taken orally. However, through injection of the compound, it could provide an alternative for those that are resistant to other HIV-1 therapies.

9 Root, M.J. *et al.* (2001) Protein design of an HIV-1 entry inhibitor. *Science* 10.1126/science.1057453 (http://www.scienceexpress.org)

Novel interleukin a sore point in psoriasis

The discovery of a novel interleukin with a role in the pathogenesis of psoriasis has recently been published[10]. The human gene that encodes interleukin-20 (IL-20) was identified by researchers at Zymogenetics (Seattle, WA, USA) by using bioinformatics to identify novel genes that encode proteins with therapeutic implications.

Researchers at Zymogenetics have characterized the interaction between IL-20 and a cell surface receptor consisting of two subunits, IL-20Rα and IL-20Rβ, present in skin cells. This association was first identified by the stimulation of human keratinocyte activation by IL-20 and the striking similarity between the skin of mice that overproduce IL-20 and human psoriatic skin, and has been further proved by the finding that the expression of both ILR subunits is increased in psoriatic skin. Animal models are now being used by the company to determine whether inhibition of the IL-20 ligand will alter the pathogenesis of psoriasis.

This latest research exemplifies the capabilities of bioinformatics in the identification of novel ligands and the coupling of this information to the discovery of novel receptors, and follows the previous identification of the interleukin-21 ligand–receptor pair using similar methodologies[11].

10 Blumberg, H. *et al*. (2001) Interleukin 20: discovery, receptor identification and role in epidermal function. *Cell* 104, 9–19

11 Parrish-Novak, J. *et al*. (2000) Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. *Nature* 408, 52–63

Great things can come in small packages

The genomics research alliance between Millennium Pharmaceuticals (Cambridge, MA, USA) and Bayer AG (Wuppertal, Germany) has resulted in the rapid discovery of a small-molecule drug candidate, the first of its kind to be found against a genomics-driven target. The time period between gene discovery and clinical status was 18 months.

Millennium's high-throughput gene discovery platform was used to profile new

Markets

Huge growth in proteomics technology market predicted

A recent report has predicted a rapid growth in the proteomics technology industry during the next decade. The report by Jain PharmaBiotech (Basel, Switzerland), entitled *Proteomics technologies and commercial opportunities*, has estimated the current collective value of the markets for proteomic technologies at ~US$2 billion. This is predicted to increase to US$6 billion by the year 2005 and US$10 billion by the year 2010.

There has been a substantial growth in potential drug targets since the completion of the Human Genome Project, but further validation of these targets is required through the use of proteomics. Several new high-throughput technologies have recently been developed for proteome analysis, production of protein-specific detection reagents, and high-resolution, highly reproducible separation platforms.

Future proteomics technologies and fields predicted to have great potential include protein chips for molecular diagnostic applications and drug target screening, and toxicoproteomics for the evaluation of protein expression to increase the understanding of toxic events for preclinical drug safety.

Early commercial planning as important for sales as shortening R&D time

Marketing and sales activity ideally should start 2–3 years before the launch of a product, concludes a report recently released by the Tufts Center for the Study of Drug Development entitled *Analysis and insight into critical drug development issues*. The report recommends that global sales teams become involved in a product's development as early as its Phase III clinical trials if they want to achieve peak sales. This joint approach of R&D and marketing and sales teams should then continue throughout launch and post-launch if sales are to be maximised sooner rather than later. Life cycle management of the drug should also be employed to ensure that improved speed to market and speed to peak sales produces a greater level of total sales.

genes in different tumour models, from which a novel gene and protein was identified and linked to cancer. Using their proprietary ultra-high-throughput methods, Bayer developed screening assays to screen its chemical library against the new protein. The novel chemical compound discovered was then optimized through tumour-specific *in vitro* and *in vivo* studies to advance it to clinical candidate status.

Millennium and Bayer report that their rapid, joint discovery program confirms the potential success of the genomics-based approach to drug discovery and eventually could hasten the development of breakthrough therapies.

New high-throughput SNP technology for target discovery

A novel procedure to discover and rapidly characterize functional single nucleotide polymorphisms (fSNPs) has been developed and patented by GenOdyssee (Les Ulis, France; http://www.genodyssee.com). Experts agree that most mutations that predispose people to disease or confer resistance to disease will be represented by fSNPs. By identifying and characterizing these fSNPs, it is hoped that therapeutics and diagnostic kits can be developed to prevent disease or stimulate the resistance that fSNPs confer.

In this latest procedure, GenOdysee address the biological relevance of SNPs before progressing to large genotyping studies, so that only SNPs that have an impact on protein function and expression are studied further. The screening of 20 cytokines has resulted in the discovery of four alleles that modify cytokine activity, one of which alters the activity of a cytokine by 50%. These results, the methodology and the diagnostic and therapeutic applications associated with every fSNP identified have been patented by the company in Europe and the USA. GenOdyssee intend to screen 45 cytokines before March 2001 and file patents for the fSNPs and resulting drug targets.

A database of all SNPs, including fSNPs and promoter variants, found by the company is to be proposed to pharmaceutical partners, particularly those involved in drug development for autoimmune, inflammatory and infectious disease, cancer, diabetes and myocardial infarction, for which the involvement of cytokines has been implicated. Arrangements for milestone payments and royalties will be negotiated for products developed from the database. It was emphasized, however, that although the database constitutes a highly competitive source of information for drug development, it does not eliminate the requirement for large genotyping studies for target validation.

Miscellaneous

Key HGP technology infringes patents

All of Applied Biosystems Big Dye™ products, sold by Applied Biosystems and used by Celera Genomics, infringe the claims of US patent 5688648 held by Amersham Pharmacia Biotech (APBiotech), it has been ruled by a California District Judge. The technology, used by Applied Biosystems and Celera in their Human Genome Project sequencing work, was ruled to infringe the proprietary energy transfer dye labeling technologies exclusively licensed to APBiotech by the University of California, Berkeley (CA, USA). The introduction of such HTS technologies in the mid-1990s significantly hastened the completion of the Human Genome Project. The court case is due to proceed to full trial by jury.

First HTS drug candidates reach clinical trials

HTS has become an integral part of the drug discovery process in many pharmaceutical and biotechnology companies but has been expensive to implement. Furthermore, because it is generally anticipated that it takes approximately ten years for a screened drug candidate to reach clinical trials, the true value of HTS is yet to be determined given the short timeframe that it has been in use. However, directors of 50 HTS laboratories participating in the study High-throughout screening 2000: New trends and directions (HighTech Business Decisions, Moraga, California, USA) have identified 46 drug candidates that are currently being tested on humans that originated from their HTS laboratories. The original screening of these drugs range from 1992 to 1998, showing a significant reduction in the ten-year estimate.

Setting standards

Incyte Genomics (Palo Alto, CA, USA) and the Gene Ontology Consortium have initiated a collaboration to develop scientific criteria for describing and querying gene functions. This collaboration, named the Gene Ontology Project (Stanford University, Stanford, CA, USA), aims to develop a standard ontology for use across single-organism databases. Michael Ashburner (European Bioinformatics Institute, Cambridge, UK) said, 'One of the major challenges facing genomic research today is that of integrating sequence data with the vast and growing body of data from functional analyses of genes.' This ontology would therefore provide a powerful tool for the scientific community to explore the functional aspects of the genomes in different organisms. Ashburner also anticipates that this project will aid the discovery of the function of new sequences.

The Gene Ontology Consortium comprises several academic, governmental and commercial groups, its objective being to generate a universal language that eases the transfer of information between those involved in gene identification. Incyte Genomics is providing funding for the project, which will go directly to the Department of Genetics (wherein the Gene Ontology Project is headed by J. Michael Cherry) at Stanford.

Keeping up appearances

Researchers at the University of North Carolina (Chapel Hill, NC, USA) have created a liquid form of DNA, which will further our understanding of DNA, and improve genetic engineering and microelectronic circuitry[12]. The DNA was liquefied by combining negatively charged DNA crystals with positively charged molten metal complexes containing ethylene oxide tails.

It has yet to be determined how the DNA structure affects the electrical and macroscopic properties of the liquid. The researchers have, to date, only used very long DNA in its helical form, but are going to investigate the effect of shortening the molecules or changing their shape. Further, the liquid DNA is also soluble in a variety of solvents in which ordinary DNA is insoluble.

'For the first time, we were able to observe how the DNA affected current

flow during oxidation and how the DNA was oxidized in a process known as mediated electrocatalysis,' said Royce Murray, Kenan Professor of Chemistry at the University of North Carolina. 'That process is a well-known phenomenon in fluids, but it has never been observed before in a biological molecule like DNA in a semi-solid environment.'

12 Leone, A.M. *et al.* (2001) An ionic liquid form of DNA: redox-active molten salts of nucleic acids. *J. Am. Chem. Soc.* 123, 218–222

US website to offer genetic counselling

A website currently undergoing trials in the US will offer its users personalized information and advice relating to their risk of developing inherited diseases, announced its server provider e-Net Software (Bristol, UK). The website, FamilyGenetix, has already passed initial testing in the UK and is looking to now form arrangements with US health insurance companies. Once established, it is expected that the site will expand to cover UK institutions. Genetic counselling is a well-established field that can save lives by making people aware of any hereditary predispositions to disease that they might have. The data in the website will be highly confidential and will be protected by password and anti-hacking technology. The website will also give users the option of speaking to a qualified professional.

News in Brief was written by *Joanna Owens, Annabel Hinde, Ben Ramster and Rebecca N. Lawrence*

People

New appointment for genomics and liquid handling at Zymark

Mark S. Spector has been appointed as Business Unit Manager for Genomics and Liquid Handling at Zymark Corporation (Hopkinton, MA, USA) and will oversee the strategic and tactical direction of this area of the business, including the management of product lines and their growth. This is a newly created role and combines the tasks of the previous Liquid Handling Product Manager and Segment Manager for Drug Discovery and Screening.

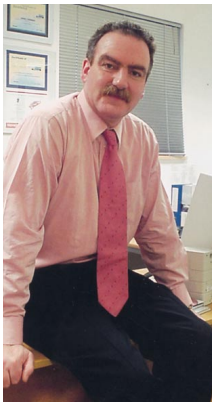
Spector comes to Zymark from being Product Manager for Genetic Analysis and Automated Solutions at Beckman Coulter (Fullerton, CA, USA) and has a background in business development, sales and negotiation, drug discovery, high-throughput automation and point-of-care diagnostics.

Regional head at LJL Biosystems moves to Gyros

Richard Millett has recently taken up the position of Vice-President of Sales Worldwide for Gyros AB (Uppsala, Sweden). Millett has previously worked as Managing Director and Vice-President of European Operations at LJL Biosystems. His new role will involve establishing a subsidiary of Gyros in the UK and to further develop the company's international sales operation.

Per Sjöberg, Vice-President of Commercial Operations of Gyros in Uppsala, Sweden said that, 'He has been highly successful in building up a number of businesses in the pharmaceutical and biotechnology market, beginning with Biacore AB and, more recently, as a regional head at LJL Biosystems. His experience in working globally at senior level in rapidly growing companies will greatly strengthen the further development of our marketing and sales organization.'

New CEO for hits-to-leads company



Anthony Baxter has recently been appointed as CEO of Argenta Discovery Ltd (Dagenham, UK), after being Chief Scientific Officer and Chairman of the Scientific Advisory Board at Oxford Asymmetry International since February 1999. Baxter is a Chartered Chemist and a Fellow of the Royal Society of Chemistry. He was Principal Research Scientist at Glaxo Group Research (Greenford, UK) until 1990, and then took on the role of Laboratory Manager with Ciba-Geigy Central Research (now Novartis; Macclesfield, UK). Subsequently, Baxter joined Oxford Diversity (Abingdon, UK) in 1994 as Director of Combinatorial Chemistry, which later became Oxford Asymmetry International.

Argenta Discovery Ltd is a new company that works under contract to convert hits and leads from HTS screens into validated patentable lead series. The company was formed from a three-way partnership of Imperial College of Science, Technology and Medicine (London, UK), a management buy-out team from Aventis Pharma AG and a syndicate of venture capitalists.

Management reorganization at CAT

Cambridge Antibody Technology (CAT; Melbourn, UK) has rearranged its management structure to fit into the increasingly diverse activities covered by the company. This has led to the appointments of Jason Avery, Nigel Burns and Diane Mellett to Senior Vice-Presidents of Business Alliances, Preclinical and General Counsel, respectively. In turn, Alex Duncan has been promoted to Vice-President of Drug Discovery, Jon Green to Vice-President of Operations and Duncan Casson to Vice-President of Project Management. Finally, Kevin Johnson who has been CAT's Research Director, has been promoted to Chief Technology Officer and is charged with the responsibility of expanding CAT's efforts in the further exploitation and development of its antibody technology platform.

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